

## Connecting via Winsock to STN

Welcome to STN International! Enter x:x

LOGINID: ssspta1644pnh

**PASSWORD :**

TERMINAL (ENTER 1, 2, 3, OR ?):2

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

FILE 'HOME' ENTERED AT 17:58:47 ON 06 OCT 2005

=> file medline embase biosis scisearch caplus  
COST IN U.S. DOLLARS SINCE FILE TOTAL  
SESSION  
FULL ESTIMATED COST ENTRY 0.21 0.21

FILE 'MEDLINE' ENTERED AT 17:58:59 ON 06 OCT 2005

FILE 'EMBASE' ENTERED AT 17:58:59 ON 06 OCT 2005  
Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 17:58:59 ON 06 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE 'SCISEARCH' ENTERED AT 17:58:59 ON 06 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE 'CPLUS' ENTERED AT 17:58:59 ON 06 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

=> s VEGF-D  
L1 983 VEGF-D  
  
=> s l1 and brain tumor  
L2 13 L1 AND BRAIN TUMOR  
  
=> dup remove l2  
PROCESSING COMPLETED FOR L2  
L3 5 DUP REMOVE L2 (8 DUPLICATES REMOVED)  
  
=> d l3 1-5 cbib abs  
  
L3 ANSWER 1 OF 5 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on  
STN DUPLICATE 1  
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1  
modulates malignant features of glioma cells. Debinski W (Reprint); Gibo  
D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr  
Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157 USA  
(Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr  
Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest  
Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens  
Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept  
Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem,  
NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005)  
Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER  
RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.  
Language: English.  
\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*  
AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are  
non metastasizing but locally infiltrating, hypervasculatized  
brain tumors of poor prognosis. We found previously  
that a c-fos-inducible vascular endothelial growth factor D is  
ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and  
that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1)  
rather than the c-Fos. We have thus become interested in the role Fra-1  
may play in malignant glioma progression/maintenance, because Fra-1 has  
the capacity to modulate transcription of a variety of target genes. In  
this work, we have analyzed the biological effects of ectopic Fra-1  
expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1  
induced prominent phenotypic changes in all three malignant glioma cell  
lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected  
in cells becoming more elongated with larger number of cellular processes.  
Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor  
xenografts, to regain tumorigenic capacity. The genotype of these cells  
changed too, because 50 of 1,056 genes examined became either up- or  
down-regulated. Conversely, Fra-1 knockdown altered prominently the  
morphology, anchorage-independent growth, tumorigenic potential, and Fra-1  
effector expression, such as vascular endothelial growth factor D, in HGG  
cells. For example, cells transfected with antisense fra-1 showed shorter  
cellular processes than the control cells that did not grow in agar, and  
their tumorigenic potential was significantly diminished. Thus, Fra-1 may  
likely play an important role in the maintenance/progression of malignant  
gliomas and potentially represents a new target for therapeutic  
interventions.

L3 ANSWER 2 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN  
2005:124071 Document No.: PREV200500122163. 1st European Conference on Tumor

Angiogenesis and Antiangiogenic Therapy, Munich, Germany, October 1-3, 2004. Anonymous. *Angiogenesis*, (2004) Vol. 7, No. Suppl. 1, pp. 1-53. print.

Meeting Info.: 1st European Conference on Tumor Angiogenesis and Antiangiogenic Therapy. Munich, Germany. October 01-03, 2004.

ISSN: 0969-6970 (ISSN print). Language: English.

AB This meeting on angiogenesis consists of 2 keynote lectures, 26 oral presentations and 64 meeting posters written in English. Different cancer types, together with their pathology, drug therapy, radiotherapy, prevention and control and gene therapy are discussed. Other topics include tumor metastasis, embryonic lymphangiogenesis, growth factor regulation and microvessel density. Tumor phenotype, drug development and antiangiogenic effect are also discussed.

L3 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN 2003:492648 Document No.: PREV200300487100. *Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors*. Debinski, Waldemar [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. *Epigenetics in cancer prevention: Early detection and risk assessment*. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: *Annals of the New York Academy of Sciences*.

Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH).

ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L3 ANSWER 4 OF 5 MEDLINE on STN DUPLICATE 2  
2003204925. PubMed ID: 12724228. *Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors*. Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . *Annals of the New York Academy of Sciences*, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable **brain tumors**. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of **brain tumors**. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in

preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of **brain tumors** or for monitoring their progression following initial treatment.

L3 ANSWER 5 OF 5 MEDLINE on STN DUPLICATE 3  
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.  
AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and locally infiltrating **brain tumor** of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of VEGF family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=> s glioblastoma  
L4 46908 GLIOBLASTOMA  
  
=> s 14 and VEGF  
L5 970 L4 AND VEGF  
  
=> s 15 and VEGF-D  
L6 16 L5 AND VEGF-D  
  
=> dup remove 16  
PROCESSING COMPLETED FOR L6  
L7 9 DUP REMOVE L6 (7 DUPLICATES REMOVED)  
  
=> d 17 1-9 cbib abs

L7 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
2005:540647 Document No. 143:90991 Single-domain protein inhibitors of type 2 vascular endothelial growth factor receptors for treatment of hyperproliferative disorders. Chen, Yan; Getmanova, Elena; Wright, Martin

C.; Harris, Al; Lim, Ai Ching; Gokemeijer, Jochim (Compound Therapeutics, Inc., USA). PCT Int. Appl. WO 2005056764 A2 20050623, 136 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IS, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US40885 20041206. PRIORITY: US 2003-2003/PV527886 20031205.

AB The present disclosure relates to novel vascular endothelial growth factor receptor (VEGFR)-binding polypeptides and methods for using these polypeptides to inhibit biol. signaling mediated by vascular endothelial growth factors (VEGFs). These VEGFR-inhibiting polypeptides may be used to inhibit hyperproliferative disorders, e.g., autoimmune disorders, inflammatory disorders, retinopathy, and cancers. Thus, sequence variants of human fibronectin III domain 3 were prepared. Some of the variants inhibited VEGF binding to VEGFR2 with picomolar KD. Such proteins also inhibited VEGFR2 signaling in mammalian cells and inhibited growth of melanoma and glioblastoma cells in vivo. PEGylation of these proteins improved their pharmacokinetics.

L7 ANSWER 2 OF 9 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on STN  
DUPLICATE 1

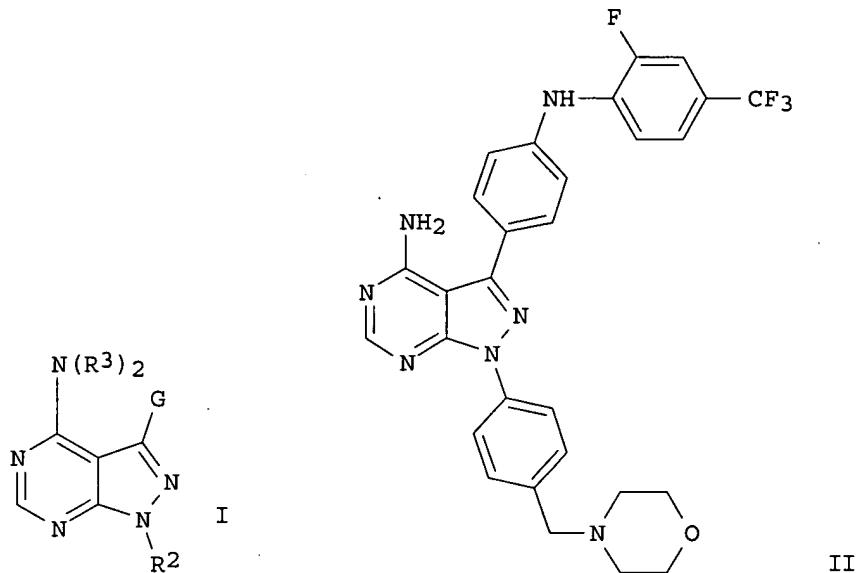
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1 modulates malignant features of glioma cells. Debinski W (Reprint); Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157 USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005) Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA. Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervasculatized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L7 ANSWER 3 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
 2002:793426 Document No. 137:310925 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott G.m.b.H. & Co. K.-G., Germany). PCT Int. Appl. WO 2002080926 A1 20021017, 867 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US9104 20020322. PRIORITY: US 2001-2001/815310 20010322.

GI

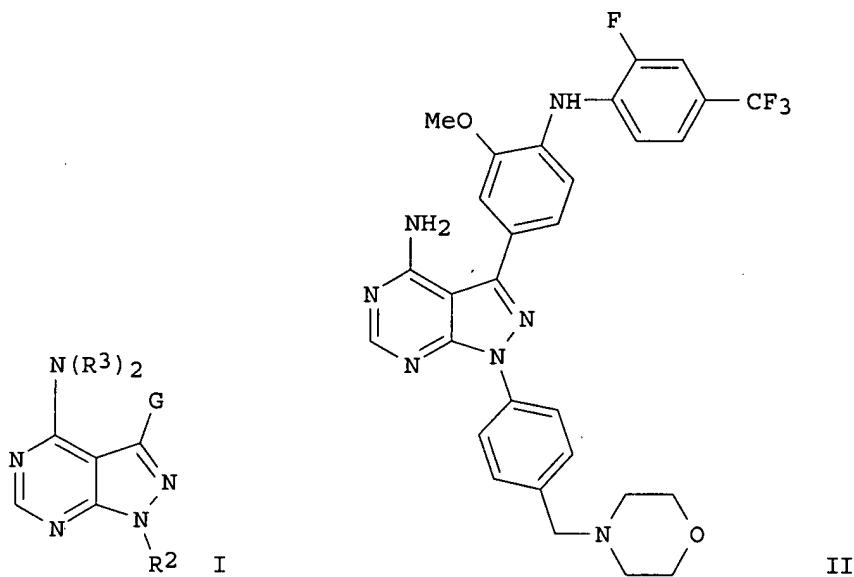


AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh3)4, and Na2CO3 in H2O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of  $\leq$  50  $\mu$ M. Certain compds. of the invention also significantly inhibited cdc2 or cellular

VEGF-induced KDR tyrosine kinase phosphorylation at concns. of  $\leq 50 \mu\text{M}$ . Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 4 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
2002:754390 Document No. 137:263056 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott GmbH & Co. KG, Germany). PCT Int. Appl. WO 2002076986 A1  
20021003, 440 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English).  
CODEN: PIXXD2. APPLICATION: WO 2002-US8996 20020322. PRIORITY: US  
2001-2001/PV278047 20010322.

GI



AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared. For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Na<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the

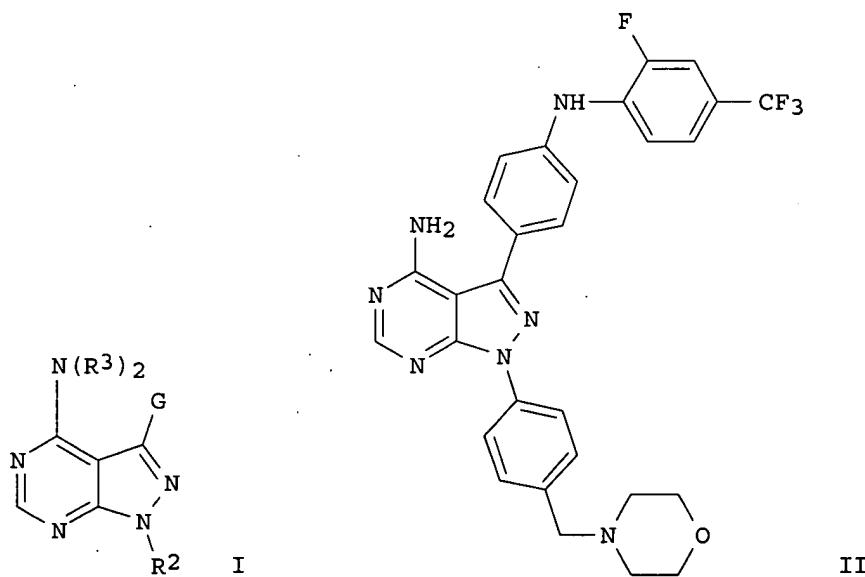
benzaldehyde in the presence of Na(AcO)3BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of  $\leq 50 \mu\text{M}$ . Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine phosphorylation at concns. of  $\leq 50 \mu\text{M}$ . Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 5 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
 2002:637486 Document No. 137:164115 VEGF-D expression in brain cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB VEGF-D serves as a target for diagnosing and treating glioblastoma multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of VEGF-D in the sample. Brain cancer is treated by modulating VEGF-D gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with VEGF-D binding to a VEGF-D receptor.

L7 ANSWER 6 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
 2002:814851 Document No. 137:310930 Preparation of 3-(azahetero)aryl-1H-pyrazolo[3,4-d]pyrimidin-3-amines as protein kinase inhibitors with antiangiogenic properties. Hirst, Gavin C.; Rafferty, Paul; Ritter, Kurt; Calderwood, David; Wishart, Neil; Arnold, Lee D.; Friedman, Michael M. (Abbott Laboratories, USA). U.S. Pat. Appl. Publ. US 2002156081 A1 20021024, 426 pp., Cont.-in-part of U.S. Ser. No. 663,780. (English). CODEN: USXXCO. APPLICATION: US 2001-815310 20010322. PRIORITY: US 1999-PV154620 19990917; US 2000-2000/663780 20000915.

GI



AB Title compds. I [wherein G = (un)substituted 5-6 membered (azahetero)aryl; R2 = H or (un)substituted trityl, cycloalkenyl, azaheteroaryl, or C6H4-4-CH2E; E = (un)substituted alkyl-OR, alkyl-CO2R, alkylheteroaryl, alkylheterocycloalkyl, or alkyl-NR2; R = independently H or (un)substituted (cyclo)alkyl, or aryl(alkyl); R3 = independently H, OH, or (un)substituted alkyl, alkyl-CO, (hetero)aryl-CO, or alkoxy; or racemic diastereomeric mixts., optical isomers, pharmaceutically acceptable salts, prodrugs, and/or biol. active metabolites thereof] were prepared. For example, 3-iodo-1H-pyrazolo[3,4-d]pyrimidin-4-amine was coupled with 4-fluorobenzaldehyde in the presence of NaH in DMF to give 4-(4-amino-3-iodo-1H-pyrazolo[3,4-d]pyrimidin-1-yl)benzaldehyde. Treatment of the 3-iodopyrazolopyrimidine with N-[2-methoxy-4-(4,4,5,5,-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]-2-fluoro-4-(trifluoromethyl)benzamide, Pd(PPh<sub>3</sub>)<sub>4</sub>, and Na<sub>2</sub>CO<sub>3</sub> in H<sub>2</sub>O afforded the N-[4-(pyrazolopyrimidin-3-yl)phenyl]benzamide. Addition of morpholine to the benzaldehyde in the presence of Na(AcO)<sub>3</sub>BH in dichloroethane produced II. All exemplified compds. significantly inhibited either FGFR, PDGFR, KDR, Tie-2, Lck, Fyn, Blk, Lyn, or Src at concentration of  $\leq$  50  $\mu$ M. Certain compds. of the invention also significantly inhibited cdc2 or cellular VEGF-induced KDR tyrosine kinase phosphorylation at concns. of  $\leq$  50  $\mu$ M. Thus, I are useful for the treatment of a wide variety of disease states ameliorated by the inhibition of protein tyrosine kinase activity essential for angiogenic processes (no data).

L7 ANSWER 7 OF 9 MEDLINE on STN DUPLICATE 2  
2003109214. PubMed ID: 12622137. Histone deacetylase inhibitors such as sodium butyrate and trichostatin A inhibit vascular endothelial growth factor (VEGF) secretion from human glioblastoma cells. Sawa Hiroki; Murakami Hiromi; Ohshima Yuko; Murakami Masahiro; Yamazaki Ichiro; Tamura Yasuo; Mima Tatsuo; Satone Akira; Ide Wataru; Hashimoto Ikuo; Kamada Hajime. (Oncology Research Center, Hokuto Hospital, Kisen 7-5, Inada-cho, Obihiro, Hokkaido 080-0833, Japan.. sawa@hokuto7.or.jp) . Brain tumor pathology, (2002) 19 (2) 77-81. Journal code: 9716507. ISSN: 1433-7398. Pub. country: Japan. Language: English.

AB We investigated the effects of histone deacetylase (HDAC) inhibitors such as sodium butyrate (SB) and trichostatin A (TSA) on the expression of vascular endothelial growth factor (VEGF) by human glioblastoma T98G, U251MG, and U87MG cells. The glioblastoma cells secreted three VEGF isoforms, VEGF (189), (165), and (121), although the expression levels of VEGF differed between the cell types. Treatment with either 5mM SB or 100 ng/ml TSA reduced VEGF secretion in conditioned media and reduced VEGF mRNA expression. We also studied the expression of VEGF-B, -C, and -D mRNA in human glioblastoma cells and their modulation by HDAC inhibitors. The PCR products of VEGF-B (357bp), VEGF-C (501bp), and VEGF-D (484bp) were amplified in all glioblastoma cells examined. Treatment with SB reduced the expression of VEGF-D mRNA in U251MG cells and the expression of VEGF-B mRNA in U87MG cells. TSA treatment reduced the expression of VEGF-D in U251MG cells. These results suggest that HDAC inhibitors reduce VEGF secretion and modulate the expression of the other VEGF family members, and therefore may inhibit angiogenesis in glioblastoma tissues.

L7 ANSWER 8 OF 9 CAPLUS COPYRIGHT 2005 ACS on STN  
2003:439275 Document No. 139:83053 VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3.

ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L7 ANSWER 9 OF 9 MEDLINE on STN

DUPLICATE 3

2002052394. PubMed ID: 11778649. VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervasculatized and locally infiltrating brain tumor of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (VEGF-D), is the newest mammalian member of VEGF family. We analyzed VEGF-D in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of VEGF-D, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously VEGF-D, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced VEGF-D expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and VEGF-D levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because VEGF-D activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The VEGF-D system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=> s (debinski w?/au)

L8 517 (DEBINSKI W?/AU)

=> s 18 and brain cancer

L9 15 L8 AND BRAIN CANCER

=> dup remove 19

PROCESSING COMPLETED FOR L9

L10 4 DUP REMOVE L9 (11 DUPLICATES REMOVED)

=> d 110 1-4 cbib abs

L10 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2005 ACS on STN

2002:637486 Document No. 137:164115 VEGF-D expression in brain

cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA).

PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W:

AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF,

BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB VEGF-D serves as a target for diagnosing and treating glioblastoma multiforme and related **brain cancers**. Cancer in a brain tissue sample is detected by analyzing expression of VEGF-D in the sample. **Brain cancer** is treated by modulating VEGF-D gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with VEGF-D binding to a VEGF-D receptor.

L10 ANSWER 2 OF 4 MEDLINE on STN DUPLICATE 1  
1998250014. PubMed ID: 9590132. Novel way to increase targeting specificity to a human glioblastoma-associated receptor for interleukin 13. **Debinski W**; Gibo D M; Puri R K. (Section of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@PSGHS.EDU) . International journal of cancer. Journal international du cancer, (1998 May 18) 76 (4) 547-51. Journal code: 0042124. ISSN: 0020-7136. Pub. country: United States. Language: English.

AB Human **brain cancers** (gliomas) overexpress large numbers of a receptor for interleukin 13 (IL13), making this receptor an attractive target for anti-glioma therapies. We have recently proposed that the glioma-associated IL13 receptor is different from the one expressed on some hemopoietic and somatic cells. In an attempt to identify an even more glioma-specific target, we have used an antagonist of a related cytokine, IL4, which neutralizes the physiological effects of both IL13 and IL4 on normal cells. Here we demonstrate that the IL4 antagonist also counteracts the action of cytotoxins targeted to the IL13 receptor on normal human cells. Importantly, the IL4 antagonist does not inhibit IL13-based cytotoxins on glioma cells at all. Thus, the IL13 receptor on glioma cells can be categorized as tumor-specific in the presence of an IL4 antagonist. We conclude that IL13 receptor-directed cytotoxins can be delivered to glioma cells without being cytotoxic to normal cells.

L10 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2  
1998254729. PubMed ID: 9592393. Novel anti-brain tumor cytotoxins specific for cancer cells. **Debinski W**; Gibo D M; Obiri N I; Kealiher A; Puri R K. (Department of Surgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psghs.edu) . Nature biotechnology, (1998 May) 16 (5) 449-53. Journal code: 9604648. ISSN: 1087-0156. Pub. country: United States. Language: English.

AB The vast majority of **brain cancers** (gliomas) express a receptor (R) for interleukin 13 (IL13). In order to achieve specific targeting of the IL13R in gliomas, we have mutagenized human (h) IL13. The mutation was made to alter IL13 interaction with the shared functional IL13/4 normal tissue receptor, but not with the glioma-associated receptor. We have thus produced hIL13.E13K (glutamic acid at position 13 changed to lysine) and fused it to derivatives of *Pseudomonas* exotoxin A. The hIL13.E13K-based cytotoxins are less active on normal cells and thus less toxic, and are better antitumor agents compared with the cytotoxins containing nonmutagenized hIL13.

L10 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3  
1999034937. PubMed ID: 9815919. Human glioma cells overexpress receptors for interleukin 13 and are extremely sensitive to a novel chimeric protein composed of interleukin 13 and *Pseudomonas* exotoxin. **Debinski W**; Obiri N I; Powers S K; Pastan I; Puri R K. (The Milton S. Hershey Medical Center, The Pennsylvania State University College of Medicine, Department of Surgery, Division of Neurosurgery, Hershey, Pennsylvania 17033, USA.. debinski@debin.nsr.hmc.psu.edu) . Clinical cancer research : an official journal of the American Association for Cancer Research, (1995 Nov) 1 (11) 1253-8. Journal code: 9502500. ISSN: 1078-0432. Pub. country: United States. Language: English.

AB Recently, we have demonstrated that a spectrum of human adenocarcinoma cell lines express binding sites for interleukin 13 (IL-13). These cells are killed by a chimeric protein composed of human (h) IL-13 and a derivative of *Pseudomonas* exotoxin, PE38QQR (Debinski et al., J. Biol. Chemical, 270: 16775-16780, 1995). The cell killing was hIL-13- and hIL-4-specific, indicating that a common binding site for the two cytokines is present in several solid tumor cell lines. Herein, we report that an array of established glioma cell lines is killed by very low concentrations of hIL-13-PE38QQR, often reaching <1 ng/ml (<20 pM). Glioma cells express up to 30,000 molecules of IL-13 receptor/cell which has intermediate affinity toward hIL-13. hIL-13-PE38QQR is more active (up to 3 logs difference in cytotoxic activities) than are the corresponding chimeric toxins containing hIL-4 or hIL-6. The cytotoxic action of hIL-13-PE38QQR is blocked by an excess of hIL-13 on all cell lines studied, and it is not neutralized by hIL-4 on some of these cells. Our results show that human **brain cancers** richly express receptors for IL-13. Furthermore, the interaction detected previously between receptors for IL-13 and IL-4 on solid tumors cell lines is of a qualitatively different character in U-251 MG and U-373 MG glioma cells. The receptor for IL-13 may represent a new marker of **brain cancers** and an attractive target for anticancer therapies.

```
=> s 18 and VEGF-D
L11          14 L8 AND VEGF-D

=> dup remove 111
PROCESSING COMPLETED FOR L11
L12          6 DUP REMOVE L11 (8 DUPLICATES REMOVED)

=> d 112 1-6 cbib abs

L12 ANSWER 1 OF 6 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on
      STN                               DUPLICATE 1
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1
      modulates malignant features of glioma cells. Debinski W
      (Reprint); Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain
      Tumor Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC
      27157 USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain
      Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA;
      Wake Forest Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence,
      Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch
      Med, Dept Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr,
      Winston Salem, NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER
      RESEARCH (APR 2005) Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786.
      Publisher: AMER ASSOC CANCER RESEARCH, 615 CHESTNUT ST, 17TH FLOOR,
      PHILADELPHIA, PA 19106-4404 USA. Language: English.
      *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
```

AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervasculatized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated.

Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L12 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN 2003:492648 Document No.: PREV200300487100. *Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors.* **Debinski, Waldemar** [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. *Epigenetics in cancer prevention: Early detection and risk assessment.* print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: *Annals of the New York Academy of Sciences.* Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L12 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2  
2003204925. PubMed ID: 12724228. *Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors.* **Debinski Waldemar**; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable brain tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of brain tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of brain tumors or for monitoring their progression following initial treatment.

L12 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
2002:637486 Document No. 137:164115 VEGF-D expression in  
brain cancer in relation to diagnosis and treatment. **Debinski,**  
**Waldemar;** Gibo, Denise M. (The Penn State Research Foundation, USA).  
PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W:  
AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR,  
CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL,  
IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG,  
MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK,  
SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF,  
BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU,  
MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2.  
APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089  
20010212.

AB VEGF-D serves as a target for diagnosing and treating  
glioblastoma multiforme and related brain cancers. Cancer in a brain  
tissue sample is detected by analyzing expression of VEGF-  
D in the sample. Brain cancer is treated by modulating  
VEGF-D gene expression in cells of the cancer, and by  
inhibiting angiogenesis associated with the cancer by interfering with  
VEGF-D binding to a VEGF-D receptor.

L12 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
2003:439275 Document No. 139:83053 VEGF-D is an  
X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma  
multiforme. [Erratum to document cited in CA136:322910]. **Debinski,**  
**Waldemar;** Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.;  
Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of  
Neurosurgery/H110, Pennsylvania State University College of Medicine,  
Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United  
States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551.  
Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L12 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 3  
2002052394. PubMed ID: 11778649. VEGF-D is an  
X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma  
multiforme. **Debinski W;** Slagle-Webb B; Achen M G; Stacker S A;  
Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery,  
Pennsylvania State University College of Medicine, Hershey 17033-0850,  
USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001  
Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country:  
United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervascularized and  
locally infiltrating brain tumor of astroglial origin with a very poor  
prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic,  
and angiogenic factor, endothelial growth factor-D (VEGF-  
D), is the newest mammalian member of VEGF family. We analyzed  
VEGF-D in GBM because of its high angiogenic potential  
and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant  
brain and GBM tissue sections as well as GBM cell lines were analyzed by  
immunofluorescence for the expression of VEGF-D,  
factor VIII (endothelial cell marker), glial-fibrillary acidic protein  
(GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos  
family transcription factors, including c-Fos and Fra-1. The proteins  
were also detected by Western blots. The differences between genotypes of  
normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND  
CONCLUSIONS: GBM expressed ubiquitously VEGF-D, which  
colocalized with GFAP. Contrary to our expectations, low levels of c-Fos  
were detected in GBM cells. However, we identified another Fos family  
member, Fra-1, together with its transcriptional activation partner,  
c-Jun, as being stably up-regulated in GBM cells. Furthermore, we  
demonstrated that a fra-1 transgene induced VEGF-D  
expression in cultured cells and GBM cell stimulation evoked a sustained  
increase in both Fra-1 and VEGF-D levels. This study

reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because VEGF-D activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The VEGF-D system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=>

---Logging off of STN---

=>

Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	82.12	82.33
DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-6.57	-6.57

STN INTERNATIONAL LOGOFF AT 18:03:39 ON 06 OCT 2005

NEWS HOURS	STN Operating Hours Plus Help Desk Availability
NEWS INTER	General Internet Information
NEWS LOGIN	Welcome Banner and News Items
NEWS PHONE	Direct Dial and Telecommunication Network Access to STN
NEWS WWW	CAS World Wide Web Site (general information)

Enter NEWS followed by the item number or name to see news on that specific topic.

All use of STN is subject to the provisions of the STN Customer agreement. Please note that this agreement limits use to scientific research. Use for software development or design or implementation of commercial gateways or other similar uses is prohibited and may result in loss of user privileges and other penalties.

FILE 'HOME' ENTERED AT 18:05:14 ON 06 OCT 2005

=> file medline embase biosis scisearch caplus  
COST IN U.S. DOLLARS SINCE FILE TOTAL  
ENTRY SESSION  
FULL ESTIMATED COST 0.21 0.21

FILE 'MEDLINE' ENTERED AT 18:05:25 ON 06 OCT 2005

FILE 'EMBASE' ENTERED AT 18:05:25 ON 06 OCT 2005  
Copyright (c) 2005 Elsevier B.V. All rights reserved.

FILE 'BIOSIS' ENTERED AT 18:05:25 ON 06 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE 'SCISEARCH' ENTERED AT 18:05:25 ON 06 OCT 2005  
Copyright (c) 2005 The Thomson Corporation

FILE 'CAPLUS' ENTERED AT 18:05:25 ON 06 OCT 2005  
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.  
PLEASE SEE "HELP USAGETERMS" FOR DETAILS.  
COPYRIGHT (C) 2005 AMERICAN CHEMICAL SOCIETY (ACS)

=> s (gibo d?/au)  
L1 148 (GIBO D?/AU)

=> s 11 and VEGF-D  
L2 14 L1 AND VEGF-D

```
=> dup remove 12
PROCESSING COMPLETED FOR L2
L3          6 DUP REMOVE L2 (8 DUPLICATES REMOVED)
```

=> d 13 1-6 cbib abs

L3 ANSWER 1 OF 6 SCISEARCH COPYRIGHT (c) 2005 The Thomson Corporation on  
STN DUPLICATE 1  
2005:428915 The Genuine Article (R) Number: 917EQ. Fos-related antigen 1  
modulates malignant features of glioma cells. Debinski W (Reprint);  
**Gibo D M.** Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor  
Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157  
USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr  
Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest  
Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens  
Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept  
Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem,  
NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005)  
Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER

RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.

Language: English.

\*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS\*

AB Malignant gliomas, and high-grade gliomas (HGG) in particular, are non metastasizing but locally infiltrating, hypervasculatized brain tumors of poor prognosis. We found previously that a c-fos-inducible vascular endothelial growth factor D is ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1) rather than the c-Fos. We have thus become interested in the role Fra-1 may play in malignant glioma progression/maintenance, because Fra-1 has the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L3 ANSWER 2 OF 6 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN 2003:492648 Document No.: PREV200300487100. Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors. Debinski, Waldemar [Reprint Author]; Gibo, Denise; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. Epigenetics in cancer prevention: Early detection and risk assessment. print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences. Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L3 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 2  
2003204925. PubMed ID: 12724228. Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors. Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable brain tumors. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as

being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of brain tumors. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of brain tumors or for monitoring their progression following initial treatment.

L3 ANSWER 4 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
2002:637486 Document No. 137:164115 VEGF-D expression in brain cancer in relation to diagnosis and treatment. Debinski, Waldemar; Gibo, Denise M. (The Penn State Research Foundation, USA). PCT Int. Appl. WO 2002064097 A2 20020822, 43 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5044 20020212. PRIORITY: US 2001-PV268089 20010212.

AB VEGF-D serves as a target for diagnosing and treating glioblastoma multiforme and related brain cancers. Cancer in a brain tissue sample is detected by analyzing expression of VEGF-D in the sample. Brain cancer is treated by modulating VEGF-D gene expression in cells of the cancer, and by inhibiting angiogenesis associated with the cancer by interfering with VEGF-D binding to a VEGF-D receptor.

L3 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2005 ACS on STN  
2003:439275 Document No. 139:83053 VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. [Erratum to document cited in CA136:322910]. Debinski, Waldemar; Slagle-Webb, Becky; Achen, Marc G.; Stacker, Steven A.; Tulchinsky, Eugene; Gillespie, G. Yancey; Gibo, Denise M. (Division of Neurosurgery/H110, Pennsylvania State University College of Medicine, Hershey, PA, 17033-0850, USA). Molecular Medicine (Baltimore, MD, United States), 7(12), 861 (English) 2001. CODEN: MOMEF3. ISSN: 1076-1551. Publisher: Johns Hopkins University Press.

AB On the cover, "mutliforme" should be "multiforme".

L3 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 3  
2002052394. PubMed ID: 11778649. VEGF-D is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervasculatized and locally infiltrating brain tumor of astroglial origin with a very poor

prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (VEGF-D), is the newest mammalian member of VEGF family. We analyzed VEGF-D in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of VEGF-D, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously VEGF-D, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced VEGF-D expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and VEGF-D levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because VEGF-D activates VEGF receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The VEGF-D system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

```
=> s 11 and VEGF
L4           14 L1 AND VEGF

=> s 14 and brain tumor
L5           12 L4 AND BRAIN TUMOR

=> dup remove 15
PROCESSING COMPLETED FOR L5
L6           4 DUP REMOVE L5 (8 DUPLICATES REMOVED)

=> d 16 1-4 cbib abs

L6   ANSWER 1 OF 4  SCISEARCH  COPYRIGHT (c) 2005 The Thomson Corporation on
      STN
DUPLICATE 1
2005:428915  The Genuine Article (R) Number: 917EQ. Fos-related antigen 1
modulates malignant features of glioma cells. Debinski W (Reprint);  

Gibo D M. Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor  

Ctr Excellence, Comprehens Canc Ctr, Med Ctr Blvd, Winston Salem, NC 27157  

USA (Reprint); Wake Forest Univ, Sch Med, Dept Neurosurg, Brain Tumor Ctr  

Excellence, Comprehens Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest  

Univ, Sch Med, Dept Radiat Oncol, Brain Tumor Ctr Excellence, Comprehens  

Canc Ctr, Winston Salem, NC 27157 USA; Wake Forest Univ, Sch Med, Dept  

Canc Biol, Brain Tumor Ctr Excellence, Comprehens Canc Ctr, Winston Salem,  

NC 27157 USA. debinski@wfubine.edu. MOLECULAR CANCER RESEARCH (APR 2005)  

Vol. 3, No. 4, pp. 237-249. ISSN: 1541-7786. Publisher: AMER ASSOC CANCER  

RESEARCH, 615 CHESTNUT ST, 17TH FLOOR, PHILADELPHIA, PA 19106-4404 USA.  

Language: English.
*ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*
AB      Malignant gliomas, and high-grade gliomas (HGG) in particular, are  

non metastasizing but locally infiltrating, hypervasculatized  

brain tumors of poor prognosis. We found previously  

that a c-fos-inducible vascular endothelial growth factor D is  

ubiquitously up-regulated in HGG grade IV, glioblastoma multiforme, and  

that glioblastoma multiforme overexpress Fos-related antigen 1 (Fra-1)  

rather than the c-Fos. We have thus become interested in the role Fra-1  

may play in malignant glioma progression/maintenance, because Fra-1 has
```

the capacity to modulate transcription of a variety of target genes. In this work, we have analyzed the biological effects of ectopic Fra-1 expression or Fra-1 knockdown in malignant glioma cells. Ectopic Fra-1 induced prominent phenotypic changes in all three malignant glioma cell lines examined: H4, U-87 MG, and A-172 MG. These changes were reflected in cells becoming more elongated with larger number of cellular processes. Furthermore, Fra-1 transgene caused H4 cells, which do not form tumor xenografts, to regain tumorigenic capacity. The genotype of these cells changed too, because 50 of 1,056 genes examined became either up- or down-regulated. Conversely, Fra-1 knockdown altered prominently the morphology, anchorage-independent growth, tumorigenic potential, and Fra-1 effector expression, such as vascular endothelial growth factor D, in HGG cells. For example, cells transfected with antisense fra-1 showed shorter cellular processes than the control cells that did not grow in agar, and their tumorigenic potential was significantly diminished. Thus, Fra-1 may likely play an important role in the maintenance/progression of malignant gliomas and potentially represents a new target for therapeutic interventions.

L6 ANSWER 2 OF 4 BIOSIS COPYRIGHT (c) 2005 The Thomson Corporation on STN 2003:492648 Document No.: PREV200300487100. **Epigenetics in high-grade astrocytomas: Opportunities for prevention and detection of brain tumors.** Debinski, Waldemar [Reprint Author]; Gibo, Denise ; Mintz, Akiva. Section of Neurosurgery, Department of Surgery, College of Medicine, Pennsylvania State University, 500 University Drive, H110, Hershey, PA, 17033-0850, USA. wdebinski@psu.edu. Verma, Mukesh [Editor, Reprint Author]; Dunn, Barbara K. [Editor, Reprint Author]; Umar, Asad [Editor, Reprint Author]. (2003) pp. 232-242. **Epigenetics in cancer prevention: Early detection and risk assessment.** print. Publisher: New York Academy of Sciences, 2 East 63rd Street, New York, NY, 10021, USA. Series: Annals of the New York Academy of Sciences. Meeting Info.: Workshop on Epigenetics in Cancer Prevention: Early Detection and Risk Assessment. Bethesda, MD, USA. December 03-04, 2001. National Institutes of Health (NIH). ISSN: 0077-8923 (ISSN print). ISBN: 1-57331-430-7 (cloth). Language: English.

L6 ANSWER 3 OF 4 MEDLINE on STN DUPLICATE 2  
2003204925. PubMed ID: 12724228. **Epigenetics in high-grade astrocytomas: opportunities for prevention and detection of brain tumors.** Debinski Waldemar; Gibo Denise; Mintz Akiva. (Department of Neurosurgery, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033-0850, USA.. wdebinski@psu.edu) . Annals of the New York Academy of Sciences, (2003 Mar) 983 232-42. Ref: 60. Journal code: 7506858. ISSN: 0077-8923. Pub. country: United States. Language: English.

AB Human high-grade astrocytomas (HGA) are the most prevalent incurable **brain tumors**. We found that the vast majority of HGA patients overexpress a restricted receptor for an immune regulatory cytokine, interleukin 13 (IL-13). Interestingly, the HGA-associated restricted receptor protein IL-13Ralpha2 is expressed in the testes, and its gene is localized to chromosome X. These mirror the expression pattern and genomic localization of cancer/testes tumor antigens (CTA). Hypothetical considerations and now experimental evidence are beginning to point towards epigenetics, and DNA methylation alterations in particular, as being responsible for the appearance in cancer of CTA, including IL-13Ralpha2. In line with our interest in the X chromosome and oncogenesis, we have identified a new ubiquitous angiogenic factor in HGA, a vascular endothelial growth factor-D (VEGF-D). We have also demonstrated that the activating protein-1 (AP-1) family of transcription factors play a potentially critical role in the progression of gliomas by eliciting uncontrolled upregulation of VEGF-D and other compounds essential for cancer cell proliferation, tumorigenesis, and infiltration. The possibility exists that an unopposed constitutive increase in AP-1 activity in HGA is related to epigenetic silencing of the

inhibitors of AP-1 activity. These phenomena offer potential targets for exploitation in either prevention or early detection of **brain tumors**. For example, anticancer vaccines against shared CTA could help in prevention of HGA development. Furthermore, drugs with anti-AP-1 activity could be effective in preventing formation/progression of HGA, or progression from less malignant lower grade gliomas to HGA. Also, circulating antibodies against CTA and factors that are AP-1 regulated may provide a useful tool in early detection of **brain tumors** or for monitoring their progression following initial treatment.

L6 ANSWER 4 OF 4 MEDLINE on STN DUPLICATE 3  
2002052394. PubMed ID: 11778649. **VEGF-D** is an X-linked/AP-1 regulated putative onco-angiogen in human glioblastoma multiforme. Debinski W; Slagle-Webb B; Achen M G; Stacker S A; Tulchinsky E; Gillespie G Y; Gibo D M. (Division of Neurosurgery, Pennsylvania State University College of Medicine, Hershey 17033-0850, USA.. wdebinski@psu.edu) . Molecular medicine (Cambridge, Mass.), (2001 Sep) 7 (9) 598-608. Journal code: 9501023. ISSN: 1076-1551. Pub. country: United States. Language: English.

AB BACKGROUND: Glioblastoma multiforme (GBM) is a hypervasculatized and locally infiltrating **brain tumor** of astroglial origin with a very poor prognosis. An X-linked c-fos oncogene-inducible mitogenic, morphogenic, and angiogenic factor, endothelial growth factor-D (**VEGF-D**), is the newest mammalian member of **VEGF** family. We analyzed **VEGF-D** in GBM because of its high angiogenic potential and its linkage to the X chromosome. MATERIALS AND METHODS: Nonmalignant brain and GBM tissue sections as well as GBM cell lines were analyzed by immunofluorescence for the expression of **VEGF-D**, factor VIII (endothelial cell marker), glial-fibrillary acidic protein (GFAP) (astrocytic cell lineage cytoplasmic marker), and several Fos family transcription factors, including c-Fos and Fra-1. The proteins were also detected by Western blots. The differences between genotypes of normal brain and GBM cells were examined by cDNA microarrays. RESULTS AND CONCLUSIONS: GBM expressed ubiquitously **VEGF-D**, which colocalized with GFAP. Contrary to our expectations, low levels of c-Fos were detected in GBM cells. However, we identified another Fos family member, Fra-1, together with its transcriptional activation partner, c-Jun, as being stably up-regulated in GBM cells. Furthermore, we demonstrated that a fra-1 transgene induced **VEGF-D** expression in cultured cells and GBM cell stimulation evoked a sustained increase in both Fra-1 and **VEGF-D** levels. This study reveals that an up-regulation of AP-1 factors may be a hallmark of GBM. Because **VEGF-D** activates **VEGF** receptor 2 and 3, receptors important for tumor angiogenesis, it may represent an X-linked/AP-1-regulated onco-angiogen in human GBM. The **VEGF-D** system and AP-1 activity appear to be very attractive targets for new molecular diagnostics and rational molecular anti-cancer therapies.

=>

---Logging off of STN---

=>  
Executing the logoff script...

=> LOG Y

COST IN U.S. DOLLARS  
FULL ESTIMATED COST

SINCE FILE ENTRY	TOTAL SESSION
37.54	37.75

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)	SINCE FILE ENTRY	TOTAL SESSION
CA SUBSCRIBER PRICE	-1.46	-1.46

STN INTERNATIONAL LOGOFF AT 18:07:08 ON 06 OCT 2005